BREAKING ADVANCES

1647  Highlights from Recent Cancer Literature

REVIEW

1649  Angiopoietin-2: An Attractive Target for Improved Antiangiogenic Tumor Therapy
Damien Gerald, Sudhakar Chintharlapalli, Hellmut G. Augustin, and Laura E. Benjamin

MEETING REPORT

1658  Ion Channels and Transporters in Cancer: Pathophysiology, Regulation, and Clinical Potential
Stine F. Pedersen and Christian Stock

PRIORITY REPORTS

1662  G-protein Inactivator RGS6 Mediates Myocardial Cell Apoptosis and Cardiomyopathy Caused By Doxorubicin
Juanqi Yang, Biswanath Maity, Jie Huang, Zhan Gao, Adele Stewart, Robert M. Weiss, Mark E. Anderson, and Rory A. Fisher

1668  Trp53 Inactivation in the Tumor Microenvironment Promotes Tumor Progression by Expanding the Immunosuppressive Lymphoid-like Stromal Network
Gang Guo, Luis Marrero, Paulo Rodriguez, Luis Del Valle, Augusto Ochoa, and Yan Cui

CLINICAL STUDIES

1666  Phase I Trial of Recombinant Modified Vaccinia Ankara Encoding Epstein–Barr Viral Tumor Antigens in Nasopharyngeal Carcinoma Patients

Précis: Vaccination of nasopharyngeal carcinoma patients targeting two pathogenic viral antigens produces potent immune responses after they have completed chemo/radiotherapy.

INTEGRATED SYSTEMS AND TECHNOLOGIES

1689  Earlier Detection of Breast Cancer with Ultrasound Molecular Imaging in a Transgenic Mouse Model
Sanitha V. Bachawal, Kristin C. Jensen, Amelie M. Lutz, Sanjiv S. Gambhir, Francois Tranquart, Lu Tian, and Jürgen K. Willmann

Précis: This study lays the foundation for the development of a novel ultrasound-based imaging approach for earlier detection of breast cancer and paves the way for translational clinical trials in the future.

1699  Collections of Simultaneously Altered Genes as Biomarkers of Cancer Cell Drug Response
David L. Masica and Rachel Karchin

Précis: New methods are offered to improve the identification of drug response biomarkers in cancer cells.

MICROENVIRONMENT AND IMMUNOLOGY

1709  Therapeutic Efficacy of Bifunctional siRNA Combining TGF-β1 Silencing with RIG-I Activation in Pancreatic Cancer
Jonathan Ellermeier, Jiwu Wei, Peter Duewell, Sabine Hoves, Mareike R. Stieg, Tina Adunka, Daniel Noerenberg, Hans-Joachim Anders, Doris Mayr, Hendrik Poeck, Gunther Hartmann, Stefan Endres, and Max Schnurr

Précis: The potency of a therapeutic siRNA can be increased by a parallel strategy to combinatorially activate an RNA helicase that triggers inflammatory responses to double-stranded viral RNA, with implications for understanding how to reprogram the tumor microenvironment to destroy tumor cells.
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<td>1721</td>
<td>LOX-Mediated Collagen Crosslinking Is Responsible for Fibrosis-Enhanced Metastasis</td>
<td>Thomas R. Cox, Demelza Bird, Ann-Marie Baker, Holly E. Barker, Melissa W-Y. Hu, Georgina Lang, and Janine T. Erler</td>
<td><strong>Précis:</strong> The fibrotic status of a metastatic niche that is determined by the extracellular matrix plays a pivotal role in determining colonization of new sites by circulating tumor cells.</td>
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<td>1733</td>
<td>Evidence for a Role of the PD-1:PD-L1 Pathway in Immune Resistance of HPV-Associated Head and Neck Squamous Cell Carcinoma</td>
<td>Sofia Lyford-Pike, Shiwen Peng, Geoffrey D. Young, Janis M. Taube, William H. Westra, Belinda Akpeng, Tullia C. Bruno, Jeremy D. Richmon, Hao Wang, Justin A. Bishop, Lieping Chen, Charles G. Drake, Suzanne L. Topalian, Drew M. Pardoll, and Sara L. Pai</td>
<td><strong>Précis:</strong> HPV-associated oropharyngeal cancers, which are increasing in incidence in the developed world, evade immune surveillance through an escape pathway that is actively being targeted in clinical trials.</td>
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<td>1742</td>
<td>IFN-γ-Mediated Downregulation of LXA4 Is Necessary for the Maintenance of Nonresolving Inflammation and Papilloma Persistence</td>
<td>Chunhui Wang, Mingjie Xiao, Xiaoman Liu, Chen Ni, Jianhong Liu, Ulrike Erben, and Zhihai Qin</td>
<td><strong>Précis:</strong> By helping resolve an inflammatory response, IFNγ blockade can promote tumor regression by reprogramming the inflammatory microenvironment.</td>
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<td>1752</td>
<td>Myeloid-Specific Expression of Ron Receptor Kinase Promotes Prostate Tumor Growth</td>
<td>Devikala Gurusamy, Jerilyn K. Gray, Peterson Pathrose, Rishikesh M. Kulkarni, Fred D. Finkleman, and Susan E. Waltz</td>
<td><strong>Précis:</strong> This study suggests a new strategy to treat prostate tumors, by blocking a tyrosine kinase that supports tumor-associated macrophages that drive immune escape.</td>
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<td>1764</td>
<td>HLA-Restricted CTL That Are Specific for the Immune Checkpoint Ligand PD-L1 Occur with High Frequency in Cancer Patients</td>
<td>Shamaila Munir, Gitte Holmen Andersen, Özcan Met, Marco Donia, Thomas Merch Freisig, Stine Kjaer Larsen, Tobias Wienfeldt Klausen, Inge Marie Svane, and Mads Hald Andersen</td>
<td><strong>Précis:</strong> PD-L1-specific cytotoxic T cells described for the first time in this study may be useful to harness for cancer immunotherapy to defeat mechanisms of immune escape used in various cancers mediated by the PD1 pathway.</td>
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<td>1777</td>
<td>A Chimeric Receptor with NKG2D Specificity Enhances Natural Killer Cell Activation and Killing of Tumor Cells</td>
<td>Yu-Hsiang Chang, John Connolly, Noriko Shimasaki, Kousaku Mimura, Koji Kono, and Dario Campana</td>
<td><strong>Précis:</strong> Findings illustrate how to increase the antitumor efficacy of NK cell therapy, a strategy that may be used to fight nearly any kind of human cancer.</td>
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<td>1787</td>
<td>Transcription Factor YY1 Contributes to Tumor Growth by Stabilizing Hypoxia Factor HIF-1α in a p53-Independent Manner</td>
<td>Shourong Wu, Vivi Kasim, Mitsunobu R. Kano, Sayaka Tanaka, Shinzuke Ohta, Yutaka Miura, Kanjiro Miyata, Xueying Liu, Ako Matsushashi, Ung-il Chung, Li Yang, Kazunori Kataoka, Nobuhiro Nishiyama, and Makoto Miyagishi</td>
<td><strong>Précis:</strong> Findings suggest a mechanistic strategy to block a core hypoxia-driven progression pathway regardless of p53 status.</td>
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<td>1800</td>
<td>Arkadia Regulates Tumor Metastasis by Modulation of the TGF-β Pathway</td>
<td>Marco A. Briones-Orta, Laurence Levy, Chris D. Madsen, Debipriya Das, Yigit Erker, Erik Sahai, and Caroline S. Hill</td>
<td><strong>Précis:</strong> An E3 ubiquitin ligase in the TGF-β signaling pathway is not required to regulate tumor growth but to colonize metastasis sites, suggesting novel antimetastatic strategies.</td>
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<td>1811</td>
<td>Phosphorylation of Ribosomal Protein S6 Attenuates DNA Damage and Tumor Suppression during Development of Pancreatic Cancer</td>
<td>Abed Khalaleh, Avigail Dreaizen, Areej Khatib, Roy Apel, Avital Swisa, Norma Kidess-Bassir, Anirban Maitra, Oded Meyuhas, Yuval Dor, and Gideon Zamir</td>
<td><strong>Précis:</strong> Findings reveal that a key mTOR effector molecule is crucial for initiation of K-Ras-induced pancreatic cancers, illuminating the centrality of this mTOR pathway to evade p53-mediated tumor suppression in this setting.</td>
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Dormant Cancer Cells Contribute to Residual Disease in a Model of Reversible Pancreatic Cancer

PREVENTION AND EPIDEMIOLOGY

MicroRNA-Related Genetic Variants Associated with Clinical Outcomes in Early-Stage Non–Small Cell Lung Cancer Patients

Genetic Variation in Transforming Growth Factor Beta 1 and Mammographic Density in Singapore Chinese Women

Identification of Inherited Genetic Variations Influencing Prognosis in Early-Onset Breast Cancer

THERAPEUTICS, TARGETS, AND CHEMICAL BIOLOGY

Focused Ultrasound Delivers Targeted Immune Cells to Metastatic Brain Tumors

Caveolin-1–LRP6 Signaling Module Stimulates Aerobic Glycolysis in Prostate Cancer
| 1912 | Mixed Lineage Kinase MLK4 Is Activated in Colorectal Cancers Where It Synergetically Cooperates with Activated RAS Signaling in Driving Tumorigenesis  
Miriam Martini, Mariangela Russo, Simona Lamba, Elisa Vitielio, Emily Hannah Crowley, Francesco Sassi, Davide Romanelli, Milo Frattini, Antonio Marchetti, and Alberto Bardelli |
| 1934 | Alkaline Phosphatase ALPL-2 Is a Novel Inhibitor of STAT3 Homodimerization Selectively Suppresses STAT3 Activity and Malignant Transformation  
Xiaolei Zhang, Ying Sun, Roberta Pireddu, Hua Yang, Murali K. Uslan, Harshani R. Lawrence, Wayne C. Guida, Nicholas J. Lawrence, and Said M. Sebti |
| 1946 | mTOR Complex 2 Is Involved in Regulation of Cbl-Dependent c-FLIP Degradation and Sensitivity of TRAIL-Induced Apoptosis  
Liqun Zhao, Ping Yue, Fadlo R. Khuri, and Shi-Yong Sun |
| 1958 | Phenotypic Profiling of DPYD Variations Relevant to 5-Fluourouracil Sensitivity Using Real-time Cellular Analysis and In Vitro Measurement of Enzyme Activity  
Steven M. Offer, Natalie J. Wegner, Croix Fossum, Kangsheng Wang, and Robert B. Diasio |
| 1969 | Involvement of Lyn and the Atypical Kinase Sgg269/PEAK1 in a Basal Breast Cancer Signaling Pathway  
| 1981 | FOXC2 Expression Links Epithelial–Mesenchymal Transition and Stem Cell Properties in Breast Cancer  
Brett G. Hollier, Agata A. Tinnirello, Steven J. Werden, Kurt W. Evans, Joseph H. Taube, Tapasree Roy Sarkar, Nathalie Sphyris, Maryam Shariati, Sreedevi V. Kumar, Venkata L. Battula, Jason I. Hershkovitz, Rudy Guerra, Jeffrey T. Chang, Naoyuki Miura, Jeffrey M. Rosen, and Sendural A. Mani |
| 1993 | Characterization of a Novel PERK Kinase Inhibitor with Antitumor and Antiangiogenic Activity  
Charity Atkins, Qi Liu, Elisabeth Minthorn, Shu-Yun Zhang, David J. Figueroa, Katherine Moss, Thomas B. Stanley, Brent Sanders, Aaron Goetz, Nathan Gaul, Anthony E. Choudhury, Hasan Alsaid, Beat M. Jucker, Jeffrey M. Asten, and Rakesh Kumar |
| 2003 | Genetic Amplification of the NOTCH Modulator LNX2 Upregulates the WNT/β-Catenin Pathway in Colorectal Cancer  
Jordi Camps, Jason J. Pitt, Georg Emons, Amanda B. Hummon, Chanelle M. Case, Marian Grade, Tamara L. Jones, Quang T. Nguyen, B. Michael Ghadimi, Tim Beisbarth, Michael J. DiFillipantonio, Natasha J. Caplen, and Thomas Ried |
ABOUT THE COVER

Inactivation of the tumor suppressor p53 frequently occurs in tumors and tumor-associated stromal cells. This study shows that p53 dysfunction in tumor-associated stroma of B16F1 melanoma favors tumor establishment and progression by promoting an inflammatory microenvironment. Using immunofluorescence, it was found that lymphoid-like fibroblastic reticular cells, which express ER-TR7 (green), GP38 (red), and α-SMA (blue), were markedly expanded in the tumor microenvironment lacking functional p53. The expansion of this specialized stromal network was associated with augmented myeloid derived suppressor cells and angiogenesis. For details, see the article by Guo and colleagues on page 1668.